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B. Webb
10/9/01

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Customer No.: 07278
PATENT TRADEMARK OFFICE

Docket No: 1225/0C675US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: David BERD

Serial No.: 09/036,645 Art Unit: 1655

Confirmation No.:

Filed: March 6, 1998 Examiner: L. ARTHUR

For: **TREATMENT OF MELANOMA WITH A VACCINE COMPRISING IRRADIATED AUTOLOGOUS MELANOMA TUMOR CELLS CONJUGATED TO A HAPTEN**

DECLARATION OF DONALD P. BRAUN, PH.D.
UNDER 37 C.F.R. § 1.132

September 27, 2001

Hon. Commissioner of
Patents and Trademarks
Washington, DC 20231

Sir:

I, Donald P. BRAUN, hereby declare and state as follows:

1. I am a citizen of the United States of America and am more than 21 years of age.

2. I presently hold the title of Administrative Director of the Medical College of Ohio Cancer Institute and Professor of Surgery at the Medical College of Ohio, 3120 Glendale Avenue, Toledo, Ohio, where I have been employed since 1999. Prior to this position, I held the positions of Director, Scientific Program Development and Professor of Medicine and Immunology/Microbiology at the Rush Cancer Institute, Rush Medical College, Chicago, Illinois. I hold a Ph.D. and M.S. degrees from the University of Illinois at the Medical Center, Chicago, and a B.S. from the University of Illinois, Urbana. I have over 25 years research experience in immunology, microbiology, and oncology, particularly cancer immunology. My qualifications are set forth more fully on the copy of my Curriculum Vitae, attached as Exhibit A.

3. I understand that Avax Therapeutics, Inc. ("Avax") has licensed certain patents and patent applications by Dr. David Berd (solely or with others) related to haptenization of tumor cells to generate an effective anti-tumor immunotherapy ("technology") from Thomas Jefferson University. I am not an employee or shareholder of Avax. My only connection with Avax is as a clinical researcher.

4. I know Dr. David Berd professionally. However, we have not collaborated on any research.

5. The law firm of Darby & Darby, attorneys for Applicant, has retained my services as an expert in connection with prosecution of these patent applications. The law firm is compensating me for my services. Thus, I have no personal interest in Avax or the patent applications.

6. I have read and am familiar with Berd et al., Proc AACR 1989;20:382 (hereinafter "Berd 1989"; a copy is attached as Exhibit B). In particular, it is my understanding that this reference has been submitted for consideration by the Examiner of this reissue application.

7. In my view as one of skill in the art in this field, the Berd 1989 abstract does not describe a haptenized melanoma tumor cell composition successfully used for vaccinating against and treatment of melanoma tumors. The abstract, like most of the abstracts presented at the AACR meetings, optimistically reports preliminary observations from a new protocol. Because the abstract omits certain details, and because by its own terms the results are preliminary, one of ordinary skill in the art would not be able to conclude from this Abstract that one could effectively treat melanoma with the described composition, much less any other type of cancer. Nothing in the Berd 1989 abstract suggests that this approach addresses fundamental questions of tumor vaccination (*e.g.*, as posed in a 1993 review on tumor vaccination written by myself and Jules Harris, M.D. for the Biotechnology Journal (Volume 1, No.

3), entitled "Cancer-Concept to Clinic" (Exhibit C)) such as: which type of immune response is most important in a host response to cancer (Exhibit C, p. 28 and Table 1); whether whole cells or extracts should be used (Id., pp. 28-29); whether to use adjuvants or cytokines (Id., p. 29); and whether an antitumor response would lead to autoimmunity (Id.). Furthermore, with respect to whole cell vaccines, questions remain as to whether to use autologous or syngeneic cells; fresh surgical specimens or cell lines; irradiation; reproducibility; and other factors (Id., p. 29, Table 2). The haptenization protocol of the Berd 1989 Abstract not only fails to address these variables, but also raises a new issue. Consequently, in 1989, one of skill in the art would not have viewed Berd 1989 as establishing an effective protocol for cancer immunotherapy.

8. By way of background, early work on developing tumor vaccines in animal models yielded successes far beyond the reality for humans. Animals used in these models are typically immunocompetent, and the tumor cell lines (unlike spontaneous tumors) bear one or more strongly immunogenic antigens. Under these circumstances, the ability to generate an immune response cannot be viewed as particularly surprising. Unlike animal models, human cancer patients are typically immunosuppressed, whether from the tumor or chemotherapy. Spontaneous human tumors bear weak immunogens. Thus the trick is to determine how to break tolerance and elicit immunity to a weak antigen in an immunosuppressed human subject. In

1992, Hanna and colleagues proposed one route, albeit based on animal data, but their results were inconclusive in humans (Exhibit C, p. 30). Berd and colleagues offered another approach, pretreatment with cyclophosphamide to inhibit suppressor T lymphocytes (Id.) In the context of these multiple approaches, it was, in 1989, unknown and unknowable whether the use of haptenized cells was a viable approach to elicit immunity to unhaptenized melanoma cells, much less that such a composition could have therapeutic potential.

9. In my view as one of skill in the art in this field, the Berd 1989 abstract does not provide a definitive protocol. The description of the vaccine is ambiguous, stating that 10-25 million cells are used. It does not state if these are given as a single injection or divided into multiple sites, nor does it specify the route of administration (*e.g.*, intradermal, subcutaneous, or intramuscular). It does not specify if the injections are given in proximity to tumor sites or even directly into the tumor site (a location that one familiar with the literature at the time would assume from a reading of this abstract, as discussed further in ¶11). It does not state how conjugation to DNP was performed or the extent of tumor cell substitution. It does not specify the ratio of tumor cells to BCG microorganisms. It also does not describe the schedule of vaccination beyond stating that vaccine or DNCB sensitization occurred 3 days following low dose cyclophosphamide i.v. administration. The statement "after 2 vaccine treatments (8 weeks)" is totally ambiguous. It is not clear if this

represented a point 4 weeks following vaccine #2, 3 weeks following vaccine #2, 2 weeks following vaccine #2, or 1 week following vaccine #2. A vaccination schedule of every 55 days could apply to what is described as readily as any of the other schedules listed above. Hanna and Peters (Cancer Research 1978;38:204-9, attached hereto as Exhibit D) emphasize the critical importance of dose, schedule, route of administration, and ratio of viable tumor cells to BCG organisms in the outcome of autologous tumor vaccines. The Berd 1989 abstract, however, provides none of these details, nor could they be deduced. Without these details, one of ordinary skill would be unable to practice the technology predictably, and furthermore would have little incentive to view this approach as any more promising than a myriad of others.

10. There is no indication in the protocol that patients have developed an immune response to unmodified cells. The opening statement of Berd 1989 indicates that a previous method practiced by Berd using non-haptenized tumor cells induced DTH to melanoma cells. But in the Berd 1989 abstract, DTH testing was done only with DNCB or DNP-modified autologous lymphocytes following patient sensitization with topical application of DNCB. The positive hapten-specific DTH reactions described in the Berd 1989 abstract are not surprising given the experience of Fujiwara (J Immunol 1980;124:863-869; attached hereto as Exhibit E), Sherman (J Immunol 1979;123:501-502; attached hereto as Exhibit F), and others using haptens to sensitize hosts against haptenized target cells. However, the vaccine

protocol of the invention, involving intradermal injection of hapten-modified autologous tumor cells, results in DTH to autologous non-haptenized tumor cells. This result could not have been anticipated nor expected from the Berd 1989 abstract taken alone or from what was known in the literature.

11. There is no convincing indication that the patients described in the Berd 1989 abstract received any clinical benefit, *i.e.*, that they were successfully treated. The descriptions of inflammatory reactions, CD4 and CD8 infiltration, and fluid accumulation over tumor lesions is no indication of clinically significant tumor regression (defined by those practiced in the art as a greater than 50% reduction in tumor size without concomitant progression in other sites). In fact, the description of lesion changes in the patients would be expected at the time of its publication, since one would presume based on Fujiwara (Exhibit D), that the patients had been sensitized to DNCB and then injected intratumorally with DNP-modified tumor cells. A skilled immuno-oncologist would have presumed that the tumor cell vaccine, which produced the described physical changes in proximity to tumor sites after only two vaccine treatments, had been administered by intratumoral injection as taught by others (while not practiced by the Berd protocol developed subsequent to the 1989 Abstract). The same outcome would have been seen if the patients had been sensitized to BCG and then injected intratumorally with BCG. Thus, the description of the lesion changes in the 1989 Abstract would be impossible to interpret as

indicative of a clinical response to a systemic vaccine. A reader would assume that a clinically meaningful tumor regression, if present, would have been reported in the abstract, and that the absence of such a report at best represented uncertainty.

12. For all of these reasons, the Berd 1989 abstract does not disclose a composition or method for the successful vaccination of melanoma cancer patients using haptenized autologous melanoma cells.

13. A final basis for the above statement can be deduced from Exhibit C. As discussed above, this review cites the work by Hanna and Hoover (references 7-9), and the work by Berd et al. employing non-haptenized melanoma cells (reference 10), among a number of hopeful, even promising, research approaches to cancer immunotherapy. Had the Berd 1989 abstract been indicative of a clinically meaningful vaccine methodology, that approach would have been considered in the review as well.

14. I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true. I further declare that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and that such willful false

statements may jeopardize the validity of the instant application or of any patent issued thereupon.

Respectfully submitted,

Date: 9/21/01

Donald P. Braun, Ph.D.

Enclosure:
Exhibit A: Curriculum Vitae of Donald P. Braun, Ph.D.
Exhibit B: Berd et al., Proc AACR1989;20:382
Exhibit C: Braun and Harris, Biotechnol J 1993;1, No. 3.
Exhibit D: Hanna et al., Cancer Research 1978;38:204-209
Exhibit E: Fujiwara et al., J Immunol 1980;124:863-869
Exhibit F: Sherman, J Immunol 1979;123:501-502